EXHIBIT M

Published in final edited form as:
J Autism Dev Disord. 2019 January ; 49(1): 376–382. doi:10.1007/s10803-018-3721-8.

Brief Report: Maternal Opioid Prescription from Preconception Through Pregnancy and the Odds of Autism Spectrum Disorder and Autism Features in Children

Eric Rubenstein[1], **Jessica C. Young**[2], **Lisa A. Croen**[3], **Carolyn DiGuiseppi**[4], **Nicole F. Dowling**[5], **Li-Ching Lee**[6], **Laura Schieve**[5], **Lisa D. Wiggins**[5], and **Julie Daniels**[2]

[1]Waisman Center, University of Wisconsin-Madison, Rm 529, 1500 Highland Avenue, Madison, WI 53705, USA

[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina Chapel Hill, 135 Dauer Dr, Chapel Hill, NC 27599, USA

[3]Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612, USA

[4]Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus School of Public Health, 13001 E. 17th Place, Aurora, CO 80045, USA

[5]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, USA

[6]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA

Abstract

Opioid use during pregnancy is associated with suboptimal pregnancy outcomes. Little is known about child neurodevelopmental outcomes. We examined associations between maternal opioid prescriptions preconception to delivery (peri-pregnancy) and child's risk of ASD, developmental delay/disorder (DD) with no ASD features, or ASD/DD with autism features in the Study to Explore Early Development, a case-control study of neurodevelopment. Preconception opioid prescription was associated with 2.43 times the odds of ASD [95% confidence interval (CI) 0.99, 6.02] and 2.64 times the odds of ASD/ DD with autism features (95% CI 1.10, 6.31) compared to mothers without prescriptions. Odds for ASD and ASD/DD were non-significantly elevated for first trimester prescriptions. Work exploring mechanisms and timing between peri-pregnancy opioid use and child neurodevelopment is needed.

Eric Rubenstein Erubenstein2@wisc.edu.

Author Contributions Study concept (Eric Rubenstein), study design and methods (all authors), statistical plan (Eric Rubenstein, Julie Daniels, Jessica Young), statistical analysis (Eric Rubenstein), statistical review and interpretation (all authors), manuscript preparation and/or review (all authors).

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest to report Eric Rubenstein had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10803-018-3721-8) contains supplementary material, which is available to authorized users.

Since study completion, Dr. Dowling has moved to the Division of Cancer Prevention and Control within CDC's National Center for Chronic Disease Prevention and Health Promotion.

Keywords

Risk factor; Opioid; ASD; Developmental disorder; Pregnancy

Prescription opioid use among pregnant women has increased concomitant with the stark rise in opioid prescribing rates in the United States between 1999 and 2015 (Desai et al. 2014; Pezalla et al. 2017); estimates in a 2000–2007 Medicaid sample found one in five pregnant women were prescribed an opioid during pregnancy (Desai et al. 2014). Although it is important to adequately treat pain conditions in pregnant women, studies have found poor outcomes for opioid use in the pregnancy period. Opioid use peri-conception is associated with increased risk of certain birth defects (Broussard et al. 2011) and neural tube defects (Yazdy et al. 2013). Opioid use during pregnancy, whether for standard pain treatment, due to addiction, or for opioid maintenance therapy, is associated with preterm birth, poor fetal growth, birth defects, congenital malformations, and poorer developmental outcomes at 6 months (Broussard et al. 2011; Whiteman et al. 2014; Norgaard et al. 2015; Lind et al. 2017; Kocek et al. 2016; Sundelin Wahlsten and Sarman 2013; Kivisto et al. 2015). Effects on longer-term developmental outcomes are still in need of study (Reddy et al. 2017).

Little is known about maternal opioid use during pregnancy and child's risk of autism spectrum disorder (ASD), developmental delay/disorder (DD) or the development of sub-diagnostic level autism traits. The development of ASD has been theorized to be impacted by endogenous opioids and oxytocin (Sahley and Panksepp 1987; Vuong et al. 2010), which may be a pathway from prenatal opioid exposure to altered fetal brain development (Bourgeron 2015; Ross et al. 2015) or suboptimal pregnancy outcomes may mediate a pathway from opioid exposure to ASD or DD (Norgaard et al. 2015). Our objective was to preliminarily examine associations between maternal opioid prescriptions during peri-pregnancy, defined as the preconception period (three months prior to conception) to the day prior to delivery and child (1) ASD, (2) developmental delay/disorder (DD) without features of autism (DD-only), or (3) either the child had ASD or the child had DD with some features of autism (ASD/DD with autism features) using data from the community-based Study to Explore Early Development (SEED). We additionally explored timing of opioid prescription and these outcomes in order to identify potential time windows of exposure for more in depth examination.

Methods

SEED is a multi-site case–control study of children ages 30–68 months examining environmental and genetic risk factors for ASD (Schendel et al. 2012). Children were eligible if they were born and resided in one of six study areas at study entry and had consent from a knowledgeable caregiver. Data were collected over two periods corresponding to SEED funding cycles: children born 2003–2006 were enrolled from 2007 to 2010 and children born 2007–2012 were enrolled from 2012 to 2016.

Case Identification

Children with ASD or other DDs were identified from multiple education and healthcare providers who serve children with DDs. A population control group (POP) was identified through random sampling of vital records at each site. All children were screened for ASD using the Social Communication Questionnaire (SCQ) (Rutter et al. 2003a), a brief parent-reported questionnaire evaluating child communication skills and social functioning, and children were given a general developmental evaluation conducted by SEED-trained clinicians. Children at risk for ASD (based on a positive SCQ score, past ASD diagnosis, or clinician suspicion of ASD during developmental evaluations) received comprehensive ASD evaluations, which included the Autism Diagnostic Interview-Revised (a parent interview on child developmental history and ASD symptoms) (Rutter et al. 2003b) and the Autism Diagnostic Observation Schedule (clinician observation of the child's ASD symptoms) (Lord et al. 2012). A SEED-developed algorithm based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision ASD criteria (American Psychiatric Association 2000) synthesized developmental assessment results and classified neurodevelopmental outcomes (Schendel et al. 2012). We subdivided children with final classification of DD (did not meet ASD criteria and were not population controls) into those with DD with negative SCQ scores and no past ASD diagnosis (DD-only) and those with positive SCQ scores or a past ASD diagnosis (DD with ASD features). Because previous SEED analyses found that children with DD with ASD features were more phenotypically similar to children with ASD than DD-only children (Wiggins et al. 2015) and because autism features can present even if an ASD diagnosis is not met (Constantino 2011), we analytically grouped children with ASD and those with DD with ASD features for some analyses (ASD/ DD with autism features). Further detail on SEED diagnostic methodology can be found in Schendel et al. 2012 and Wiggins et al. 2015.

Exposure and Covariate Assessment

Maternal prescriptions administered by healthcare providers during peri-pregnancy were abstracted from prenatal medical records. Two independent assessors examined prescriptions for opioid medications. The medical record included start and end date of prescriptions and we estimated dates of conception and trimesters using the child's gestational age on the birth record. We excluded day of delivery in an attempt to exclude prescriptions related to childbirth or post-birth recovery. A list of opioids prescribed to mothers in our sample during peri-pregnancy is provided in supplement 1. Since our exposure is opioid prescriptions, we do not include mother's who self reported illicit opioid use during pregnancy as exposed unless they also had a prescription opioid. We ran sensitivity analysis excluding mothers with illicit use to examine whether including these mothers affected our results. We presented descriptive statistics for common conditions that a mother self-reported as having taken a medication for during pregnancy and are conditions that opioids are often prescribed for (injury, back pain, migraine headaches, cough/cold that required medication). Because mothers did not consistently self-report the names of prescription medications taken (i.e. they did not report medication name or reported 'pain medication' rather than specific medication name) we were unable to verify whether these were the conditions for which the opioid was prescribed. Covariate data were collected through

caregiver interviews and surveys, birth records, and prenatal medical records. Each site received institutional review board approval.

Analytic Approach

We used unadjusted and adjusted logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CI) comparing maternal opioid prescriptions among children with ASD, DD-only, or ASD/DD with autism features to POP children. We classified time windows of opioid prescription as any prescription during peri-pregnancy, 3 months pre-pregnancy to conception, trimester 1, trimester 2, and trimester 3 through day prior to childbirth. We identified the following potential confounders based on our theoretical model and available data a priori: study site, SEED study period, maternal age (with cubic splines at 22 and 44), body mass index pre-pregnancy, and self-reported education, race/ethnicity, smoking or alcohol use during pregnancy, and psychiatric conditions pre-childbirth. To maximize precision, we used a change-in-estimate approach excluding covariates from the multivariable model that were not statistically associated with case status or opioid prescription and whose removal changed the natural log of the adjusted OR (aOR) by < 10% (Supplements 2 and 3). Our final model included SEED study period, maternal race/ethnicity, education, smoking during pregnancy, and psychiatric conditions pre-childbirth. Observations with missing data (< 1%) were dropped from adjusted models. Analyses were conducted using SAS 9.4.

Results

Our sample included 1369 children with ASD, 938 with DD-only, 476 with DD with autism features, and 1577 POP children (Table 1). Overall, 7.7% of mothers (N = 336) had been prescribed an opioid during peri-pregnancy. The percentage of mothers having prescription opioids preconception with a child in the ASD group was three times that of mothers of children in the POP group (1.2% vs. 0.4%) and the percentages were more similar later in pregnancy (third trimester 3.4% in the ASD group, 3.0% in the POP group). During peri-pregnancy, 254 mothers had one opioid prescription, 53 had two, and 29 had three or more. Most commonly prescribed opioids were hydrocodone (n = 105), oxycodone (N = 77), and codeine (N = 77). Sixteen mothers had opioid prescriptions in multiple time-periods. Eleven mothers (0.8%) self-reported illicit opioid use during the peri-pregnancy period. Although we could not link indication directly to medication, 68 mothers with an opioid prescription reported using a medication for migraine headaches during pregnancy (20.3% of all mother's with opioid prescriptions), 27 reported medication use for injury during pregnancy (8.1%), and 47 reported medication for back pain during pregnancy (14.0%). Nineteen mothers had received a prescription for an opioid with the primary active ingredient being for cough or cold symptoms (5.7%). Among mothers receiving opioid prescriptions, the presence of these indications was not different by child developmental outcome based on chi-square tests (data not shown).

Maternal opioid prescriptions prior to conception were significantly associated with increased odds of having a child with ASD/DD with autism features compared to children of mothers without opioid prescriptions (Table 2). Mothers with first trimester opioid

prescriptions had elevated but nonsignificant aORs for having a child with ASD or ASD/DD with autism features compared to children of mothers without opioid prescriptions. Associations were weak and nonsignificant for opioid prescriptions during other pregnancy periods and when DD-only was our outcome. Adjustment attenuated effects compared to unadjusted effects across models and outcomes. In sensitivity analyses, we examined precision of our change-in-estimate approach, finding the fully adjusted model had similar aORs with increasing precision after dropping non-informative covariates (Supplement 2 and 3). Results were not different in sensitivity analysis that excluded mothers with self-reported illicit opioid use (data not shown).

Discussion

Opioid use during pregnancy is a major public health concern, yet little research has examined later child developmental outcomes. In the Study to Explore Early Development, a multi-site case-control study of neurodevelopment in children 30–68 months, we found maternal opioid prescriptions preconception were associated with increased odds of child ASD/DD with autism features. ORs for ASD and ASD/ DD with autism features were higher in the first trimester comparing mothers with opioid prescriptions to those without, but 95% confidence intervals crossed the null.

Mechanistically, opioid exposure near conception and early in pregnancy may alter fetal brain structure and function, specifically synaptic plasticity and neural connectivity (Ross et al. 2015) which could promote the development of some autism traits (Bourgeron 2015). Further, exogenous opioid exposure could alter opioid receptors affecting child neurodevelopment (Gonzalez-Nunez et al. 2013; Sahley and Panksepp 1987). Opioid use may increase risk for poor pregnancy outcomes like preterm birth, preeclampsia, and intrauterine growth restriction (Norgaard et al. 2015), which then may increase ASD vulnerability (Lyall et al. 2017). This potential mechanism is illustrated by studies that find decreased scores on neurodevelopmental assessments for children who were exposed to opioids in utero (Nygaard et al. 2015) or had a mother on opioid maintenance therapy during pregnancy (Sundelin Wahlsten and Sarman 2013). Our largest effect sizes were focused in the peri-conception period, a period in which opioid exposure has been seen to be associated with increased risk of birth defects (Broussard et al. 2011), but it is difficult to deduce how other factors associated with preconception opioid use (unplanned pregnancy, indication) may impact this association. Although aORs were higher for the ASD and ASD/DD with autism features group, the DD-only group also had elevated aORs for the prescriptions in the preconception period. With larger samples with more detailed opioid information these mechanisms could be better understood with additional insight into timing as well as differentiation between general DD and specific autism traits. Further, the interactive effect of opioid exposure and genetic underpinnings of ASD could be explored.

It is possible that residual confounding or selection bias impacted results. The SEED sample is of higher socioeconomic status (DiGuiseppi et al. 2016) and may explain the lower prevalence of opioid prescription during pregnancy (7.7%) that has been reported in other studies (20–30%) (Epstein et al. 2013; Desai et al. 2014). We additionally saw much higher percentage of mothers that smoked during pregnancy in the ASD and ASD/DD with autism

features group compared to the POP group, and future analyses may be needed to explore potential interactive effects between smoking and opioid use. While our analyses adjusted for several factors known to be associated with both ASD risk and opioid prescription, such as maternal age, smoking, and maternal psychiatric conditions, our estimates could be biased due to unmeasured confounders such as yet to be discovered risk factors for both ASD and opioid prescription.

This preliminary and exploratory study was limited to opioid prescriptions captured in prenatal records and we did not have data on consumption patterns. We lacked information on dosage, duration, and indication, limiting our interpretation. Further, our analyses were likely underpowered due to the low prevalence of opioid prescriptions in our sample, leading to wide confidence intervals and potential type II error.

Despite limitations, this study is the first to assess associations between maternal opioid prescriptions and children with ASD or ASD/DD with autism features among a large, well phenotyped sample. These findings highlight the preconception and early pregnancy periods as exposure windows to focus on in future studies on the association between opioid prescriptions during pregnancy and child ASD or autism traits. Replication of this work with prospective data collection, negative controls (like pregnant women who received non-steroidal anti-inflammatory drugs), and more data on dosage and timing can help deduce etiologic mechanisms between opioid use and ASD and DD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The investigators acknowledge the contributions made to this study by project staff and enrolled families. A portion of these data were supplied by the Bureau of Health Statistics and Research—PA Department of Health Harrisburg, PA. The PA Department of Health specifically disclaims responsibility for any analysis interpretations or conclusions. This publication was supported by six cooperative agreements from the Centers for Disease Control and Prevention (CDC): Cooperative Agreement Number U10DD000180, Colorado Department of Public Health; Cooperative Agreement Number U10DD000181, Kaiser Foundation Research Institute (CA); Cooperative Agreement Number U10DD000182, University of Pennsylvania; Cooperative Agreement Number U10DD000183, Johns Hopkins University; Cooperative Agreement Number U10DD000184, University of North Carolina at Chapel Hill; and Cooperative Agreement Number U10DD000498, Michigan State University. Eric Rubenstein was additionally supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number T32HD007489 and U54 HD090256. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or NIH.

References

American Psychiatric Association. (2000). Diagnostic and statistcal manual of mental disoders (4). Arlington: American Psychiatric Publishing.

Bourgeron T (2015). From the genetic architecture to synaptic plasticity in autism spectrum disorder. Nature Reviews : Neuroscience, 16(9), 551–563. 10.1038/nrn3992. [PubMed: 26289574]

Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. (2011). Maternal treatment with opioid analgesics and risk for birth defects. American Journal of Obstetrics and Gynecology. https ://doi.org/10.1016/j.ajog.2010.12.039.

Constantino JN (2011). The quantitative nature of autistic social impairment. Pediatric Research. 69(5 Pt 2), 55R–62R, https://doi.org/10.1203/PDR.0b013 e3182 12ec6 e.

Desai RJ, Hernandez-Diaz S, Bateman BT, & Huybrechts KF (2014). Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstetrics and Gynecology, 123(5), 997–1002. 10.1097/AOG.0000000000000208. [PubMed: 24785852]

DiGuiseppi CG, Daniels JL, Fallin DM, Rosenberg SA, Schieve LA, Thomas KC, et al. (2016). Demographic profile of families and children in the Study to Explore Early Development (SEED): Case–control study of autism spectrum disorder. Disability and Health Journal, 9(3), 544–551. 10.1016/j.dhjo.2016.01.005. [PubMed: 26917104]

Epstein RA, Bobo WV, Martin PR, Morrow JA, Wang W, Chandrasekhar R, et al. (2013). Increasing pregnancy-related use of prescribed opioid analgesics. Annals of Epidemiology, 23(8), 498–503. https://doi.org/10.1016/j.annep idem.2013.05.017. [PubMed: 23889859]

Gonzalez-Nunez V, Jimenez Gonzalez A, Barreto-Valer K, & Rodriguez RE (2013). In vivo regulation of the mu opioid receptor: Role of the endogenous opioid agents. Molecular Medicine, 19, 7–17. 10.2119/molmed.2012.00318 . [PubMed: 23348513]

Kivisto K, Tupola S, & Kivitie-Kallio S (2015). Prenatally buprenorphine-exposed children: Health to 3 years of age. European Journal of Pediatrics, 174(11), 1525–1533. 10.1007/s00431-015-2562-0. [PubMed: 26003659]

Kocek M, Wilcox R, Crank C, & Patra K (2016). Evaluation of the relationship between opioid exposure in extremely low birth weight infants in the neonatal intensive care unit and neurodevelopmental outcome at 2 years. Early Human Development, 92, 29–32. 10.1016/j.earlhumdev.2015.11.001. [PubMed: 26624803]

Lind JN, Interrante JD, Ailes EC, Gilboa SM, Khan S, Frey MT, et al. (2017). Maternal use of opioids during pregnancy and congenital malformations: A systematic review. Pediatrics. 10.1542/peds.2016-4131.

Lord C, Rutter M, DiLavore PC, & Risi S (2012). Autism diagnostic observation schedule. Journal of Autism and Developmental Disorders. 30, 205–223

Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, et al. (2017). The changing epidemiology of autism spectrum disorders. Annual Review of Public Health, 38, 81–102. https ://doi.org/10.1146/annurev-publhealth-031816-044318.

Norgaard M, Nielsson MS, & Heide-Jorgensen U (2015). Birth and neonatal outcomes following opioid use in pregnancy: A Danish population-based study. Substance Abuse, 9(Suppl 2), 5–11. 10.4137/SART.S23547.

Nygaard E, Moe V, Slinning K, & Walhovd KB (2015). Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. Pediatric Research, 78(3), 330– 335. 10.1038/pr.2015.95. [PubMed: 25978800]

Pezalla EJ, Rosen D, Erensen JG, Haddox JD, & Mayne TJ (2017). Secular trends in opioid prescribing in the USA. Journal of Pain Research, 10, 383–387. 10.2147/JPR.S129553. [PubMed: 28243142]

Reddy UM, Davis JM, Ren Z, & Greene MF, Opioid Use in Pregnancy, N. A. S., & Childhood Outcomes Workshop Invited (2017). Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: Executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstetrics and Gynecology, 130(1), 10–28. 10.1097/AOG.0000000000002054.S. [PubMed: 28594753]

Ross EJ, Graham DL, Money KM, & Stanwood GD (2015). Developmental consequences of fetal exposure to drugs: What we know and what we still must learn. Neuropsychopharmacology, 40(1), 61–87. https ://doi.org/10.1038/npp.2014.147. [PubMed: 24938210]

Rutter M, Bailey A, & Lord C (2003a). SCQ: Social Communication Questionnaire. Los Angeles: Western Psychological Services.

Rutter M, Le Couteur A, & Lord C (2003b). ADI-R: Autism Diagnostic Interview-Revised.

Sahley TL, & Panksepp J (1987). Brain opioids and autism: An updated analysis of possible linkages. Journal of Autism and Developmental Disorders, 17(2), 201–216. 10.1007/BF01495056. [PubMed: 3038836]

Schendel DE, Diguiseppi C, Croen LA, Fallin MD, Reed PL, Schieve LA, et al. (2012). The Study to Explore Early Development (SEED): A multisite epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network. Journal of Autism and Developmental Disorders, 42(10), 2121–2140. https://doi.org/10.1007/s10803-012-1461-8. [PubMed: 22350336]

Sundelin Wahlsten V, & Sarman I (2013). Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. Acta Paediatrica, 102(5), 544–549. 10.1111/apa.12210 . [PubMed: 23432078]

Vuong C, Van Uum SH, O'Dell LE, Lutfy K, & Friedman TC (2010). The effects of opioids and opioid analogs on animal and human endocrine systems. Endocrine Reviews, 31(1), 98–132. 10.1210/er.2009-0009. [PubMed: 19903933]

Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, & Salihu HM (2014). Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. J Pregnancy. 2014, 906723, 10.1155/2014/906723. [PubMed: 25254116]

Wiggins LD, Reynolds A, Rice CE, Moody EJ, Bernal P, Blaskey L, et al. (2015). Using standardized diagnostic instruments to classify children with autism in the study to explore early development. Journal of Autism and Developmental Disorders, 45(5), 1271–1280. 10.1007/s10803-014-2287-3. [PubMed: 25348175]

Yazdy MM, Mitchell AA, Tinker SC, Parker SE, & Werler MM (2013). Periconceptional use of opioids and the risk of neural tube defects. Obstetrics and Gynecology, 122(4), 838–844. 10.1097/AOG.0b013e3182a6643c. [PubMed: 24084542]

Table 1.

Maternal demographics, health conditions, and behaviors and opioid prescriptions from three months preconception to one day prior to childbirth between 2003 and 2012 in the Study to Explore Early Development, by child neurodevelopmental outcome.

	ASD N=1369		DD-Only N= 938		DD with ASD features N=476		POP N=1577	
	n	%	n	%	n	%	n	%
Opioid prescription								
Peri-pregnancy[a]	126	9.2	66	7.0	48	10.1	96	6.1
Preconception[b]	17	1.2	8	0.9	6	1.3	7	0.4
First trimester	29	2.1	12	1.3	7	1.5	17	1.1
Second trimester	25	1.8	21	2.2	13	2.7	19	1.2
Third trimester	47	3.4	24	2.6	16	3.4	47	3.0
Unknown time	13	0.9	7	0.7	8	1.7	9	0.6
None	1243	90.8	872	93.0	428	89.9	1481	93.9
Maternal race/ethnicity								
White	812	59.3	673	71.8	250	52.6	1173	74.4
Black	309	22.6	133	14.2	149	31.4	210	13.3
Asian	109	8.0	38	4.1	14	2.9	80	5.1
Other/multiracial[c]	139	10.2	93	9.9	62	13.1	114	7.2
Missing			1		1			
Maternal education								
≥12 years	197	14.5	121	13.1	139	29.3	149	9.5
13–15 years	429	31.6	235	25.4	162	34.1	317	20.3
≥16 years	733	53.9	571	61.6	174	36.6	1095	70.1
Missing	10		11		1		16	
Maternal BMI pre-pregnancy								
<18.5	89	6.5	74	7.9	31	6.5	99	6.3
18.5–25	659	48.1	489	52.1	188	39.5	924	58.6
>25–30	333	24.3	199	21.2	131	27.5	339	21.5
>30	288	21.0	176	18.8	126	26.5	215	13.6
Maternal psychiatric condition pre-childbirth[d]								
Yes	349	25.6	210	22.7	129	27.5	265	16.9
No	1012	74.4	716	77.3	340	72.5	1303	83.1
Missing	8		12		7		9	
Maternal smoking during pregnancy								
Yes	212	20.0	91	9.7	97	20.4	147	9.3
No	1157	80.0	847	90.3	379	79.6	1430	90.7
Maternal alcohol use during pregnancy								
Yes	641	46.8	460	49.0	274	57.6	923	58.5
No	728	53.2	478	51.0	202	42.4	654	41.5

	ASD N=1369		DD-Only N= 938		DD with ASD features N=476		POP N=1577	
	n	%	n	%	n	%	n	%
Maternal age at childbirth								
Mean (SD)	31.6	5.5	32.4	5.5	30.1	6.2	32	5.4
Missing	3		0		0		1	
Site								
California	200	14.6	156	16.6	43	9.0	230	14.6
Colorado	269	19.6	185	19.7	67	14.1	322	20.4
Georgia	251	18.3	150	16.0	85	17.9	279	17.7
Maryland	242	17.7	93	9.9	32	6.7	234	14.8
North Carolina	224	16.4	223	23.8	137	28.8	276	17.5
Pennsylvania	183	13.4	131	14.0	112	23.5	236	15.0
Child year of birth								
2003	56	4.1	32	3.4	9	1.9	49	3.1
2004	206	15.0	242	25.8	78	16.4	343	21.8
2005	247	18.0	291	31.0	126	26.5	396	25.1
2006	139	10.2	91	9.7	59	12.4	80	5.1
2007	1	0.1	0	0.0	0	0.0	4	0.3
2008	215	15.7	102	10.9	72	15.1	155	9.8
2009	204	14.9	95	10.1	58	12.2	216	13.7
2010	189	13.8	69	7.4	40	8.4	187	11.9
2011	112	8.2	15	1.6	34	7.1	147	9.3
2012	0	0.0	1	0.1	0	0.0	0	0.0

ASD: Autism spectrum disorder

DD-only: Developmental delay/disorder without features of ASD

POP: Population controls

BMI: Body mass index

SD: Standard deviation

[a]From three months preconception to one day prior to childbirth

[b]From three months preconception to conception

[c]Includes Hispanic ethnicity

[d]Psychiatric conditions (depression, anxiety, obsessive compulsive disorder, personality disorder, schizophrenia, bipolar disorder) collected from maternal interview on past medical history

Table 2.

Unadjusted and adjusted odds ratios and 95% confidence intervals for the association between maternal opioid prescriptions in the peri-pregnancy period and child neurodevelopmental outcomes in children born from 2003 to 2012 enrolled in the Study to Explore Early Development

	Unadjusted								
	ASD N=1369			DD-Only N=938			ASD/DD with autism features[a] N=1845		
Time of use	N	OR[b]	95% CI	N	OR	95% CI	N	OR	95% CI
Peri-pregnancy[c]	126	1.56	1.19, 2.06	66	1.17	0.84, 1.62	174	1.61	1.24, 2.08
Preconception[d]	17	2.82	1.27, 6.82	8	1.92	0.70, 5.34	23	2.83	1.21, 6.62
Trimester 1	29	1.99	1.09, 3.63	12	1.19	0.57, 2.50	36	1.83	1.02, 3.26
Trimester 2	25	1.52	0.84, 2.78	21	1.88	1.00, 3.52	38	1.72	0.99, 3.00
Trimester 3	47	1.16	0.77, 1.75	24	0.85	0.52, 1.41	63	1.15	0.78, 1.69
	Adjusted[e]								
	ASD N=1359			DD-only N=927			ASD/DD with autism features N=1834		
Time of use	N	aOR	95% CI	N	aOR	95% CI	N	aOR	95% CI
Peri-pregnancy	126	1.26	0.94, 1.68	66	1.06	0.76, 1.49	174	1.30	0.99, 1.71
Preconception	17	2.43	0.99, 6.02	8	1.94	0.68, 5.52	23	2.64	1.10, 6.31
Trimester 1	29	1.58	0.85, 2.94	12	1.06	0.50, 2.28	36	1.48	0.81, 2.69
Trimester 2	25	1.13	0.61, 2.12	21	1.64	0.87, 3.12	38	1.24	0.69, 2.22
Trimester 3	47	1.02	0.66, 1.57	24	0.85	0.52, 1.41	63	0.96	0.64, 1.45

ASD: Autism spectrum disorder

DD-only: Developmental delay/disorder without features of ASD

OR: Odds ratio

aOR: Adjusted odds ratio

CI: confidence interval

[a] ASD/DD with autism features group includes children with autism spectrum disorder or non-ASD developmental delay/disorders with autism features

[b] Exposure for case groups were compared to exposure for population controls at each time of use

[c] Three months preconception to one day prior to childbirth

[d] Three months preconception to conception

[e] Adjusted for maternal education, race/ethnicity, smoking during pregnancy, psychiatric condition prior to childbirth, and SEED study period (2003 to 2006 or 2007 to 2012). Ns are smaller due to missing covariate data.